REMARKS:

Claims 61, 62, 64, 66-73, and 75-81 are in this application, no claims having been added, claims 63, 65, and 74 having been cancelled, and claims 61, 62, 64, 66-72, and 79-81 having been amended by this response. Claims 61-81 were rejected under 35 USC 103(a) and for double patenting.

The amendment

Claims 61-81 were previously pending in this application; and all claims were rejected.

Previous claims 61-81 referred generally to a lipid formulation, with claims 65 and 74 defining that formulation as a liposomal formulation. Claims 61, 62, 64, 66-72, and 79-81 have been amended to refer to a liposomal formulation with a particular lipid:compound ratio, and claims 63, 65 and 74 have been cancelled as redundant.

Claims 61 and 72 specified that the lipids of the formulation "are" egg phosphatidylcholine (EPC) and egg phosphatidylglycerol (EPG). These claims have been amended to recite that the lipids "consist of" EPC and EPG, thereby excluding the presence of other lipids. Support for this amendment can be found at page 10, lines 5-35, and Examples 4-9, showing the use of just these two lipids to form the lipid component of the liposomes (note that Examples 5 and 6 also contain comparative formulations outside the scope of the present claims).

Claims 69-71 specified that the formulation is a liposomal formulation "composed of" the active compound, EPC, EPG, and sucrose. These claims have been amended to recite that the formulation "consists essentially of" the active compound, EPC, EPG, and sucrose, thereby excluding the presence of other lipids or liposomal functional ingredients, though it is of course understood that the liposomal formulation (and even to a certain extent the lyophilized liposomal formulation) will contain aqueous components such as the water and ethanol referred to in the Examples, and may also contain e.g. a buffer. Support for this amendment can also be found at page 10 and the Examples cited above.

Claim 63 specified that the formulation had a lipid:compound ratio of 3.5-4.5:0.5-1.5 by weight. That limitation has been incorporated into claims 61 and 72.

Entry of the amendment after final rejection is requested and is believed appropriate because the amendment places the application in better condition for allowance or appeal by clarifying that the claims refer to liposomal formulations, by replacing terms considered by the Examiner (but not intended by Applicants) to be "open" with "closed" terms – such as the replacement of "are" with "consisting of" referred to above, and by limiting the lipid:compound ratio. The amended claims raise no issues of new matter, nor do they present new issues requiring further consideration or search, because they are narrower than the claims before amendment.

Applicants will sequentially address the issues raised in the Office Action, *with the paragraphs of this response numbered as in the Office Action.*

Rejections under 35 U.S.C. §103(a)

2. Claims 61-81 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Kauvar et al. (US Patent No. 5,955,432) or WO 96/40205, further in view of Yau-Young (US Patent No. 5,023,087), Lambiez et al. (US Patent No. 5,605,703), and Uster et al. (US Patent No. 4,944,948) alone or in combination. The Office Action states that both Kauvar et al. and WO 96/40205

> "disclose a method of stimulating hematopoiesis using the same claimed compounds. Although Kauvar et al. and WO do not show the administration of the compounds in liposomal form, through examples, both suggests the use of liposomes for the delivery of compounds [locations cited]. What are lacking in the references however, are the teachings of the use of specific liposomes, that is, negatively charged."

The Office Action then refers to Yau-Young as disclosing liposomal formulations for increased stability, in which the liposomes are made from egg PC and PG; to Lambiez et al. as disclosing doxorubicin-containing liposomes and teaching that the use of a negatively charged phospholipids favors stability of the liposome solution, and showing high encapsulation efficiency; and to Uster et al. as disclosing liposomal formulations for EGF using EPC and EPG in a 1:1 ratio, and that these liposomes enhance the half-life of the EGF.

This rejection as applied to amended claims 61, 62, 64, 66-73, and 75-81 is respectfully traversed.

With regard to the primary references, it is accepted that neither Kauvar et al. nor WO 96/40205 anticipate or render unpatentable claims 61, 62, 64, 66-73, and 75-81, because the Office Action notes that the references "are lacking the teachings of the use of specific liposomes". The Office Action points to Yau-Young as showing liposomal formulations made from egg PC and PG, referring:

- to the Abstract;
- to col. 7, l. 58 – col. 8, l. 18;
- to col. 9, l. 65 – col. 10, l. 49;
- to col. 16, l. 34 et seq.;

- to col. 18, l. 45 et seq.; and
- to the Examples.

However, none of the bulleted items above disclose or suggest either the liposome formulation or the ratios given in claim 61. It is accepted that Yau-Young discloses egg PC (EPC), soy PC, and egg PG (EPG) as preferred PC and PGs (col. 7, ll. 52-53), when used in conjunction with "empty" liposomes. However, taking each item in turn: the Abstract does not disclose any liposome-forming materials or ratios; col. 7, l. 58 – col. 8, l. 18, while disclosing that negatively charged phospholipids increase the rate of clearance, discloses no lipid ratios; col. 9, l. 65 – col. 10, l. 49, while disclosing the advantage of liposomal compositions, does not disclose any liposome-forming materials or ratios; col. 16, l. 34 et seq., while also disclosing the advantage of liposomal compositions, does not disclose any liposome-forming materials or ratios; and col. 18, l. 45 et seq., while disclosing uses for liposomal compositions, does not disclose any liposome-forming materials or ratios. Looking then to the Examples, Example 1 shows five lipid formulations of which three contain one or more of EPC and EPG and no other lipid, but they have EPC:EPG ratios of ∞(EPC but no EPG) in composition A, 18.8:1 in B, and 0 (EPG but no EPC) in D: all well outside the 0.75:1.25-1.25:0.75 range claimed in claim 61. No later Example shows any formulation having different lipid ratios.

Also, Yau-Young fails to disclose the use of the formulation for small peptides such as those claimed as active ingredients here – Yau-Young's only examples are of salmon calcitonin, which is a 32-amino acid polypeptide with one disulfide bond and a molecular weight around 3400, and the antibiotic gentamicin.

Furthermore, Yau-Young notes that the encapsulation efficiency for the method he used are typically as low as 10-20% whereas Applicants have found that they can achieve an encapsulation efficiency greater than 80%.

Finally, Yau-Young fails to show the very low lipid:compound ratio currently claimed.

Applicants respectfully submit that while Yau-Young does indeed show EPC:EPG liposomes, Yau-Young neither discloses nor suggests the EPC:EPG ratio and lipid:compound ratio claimed in claim 61 (and hence the dependent claims and corresponding preparation and use claims) or the encapsulation of small peptides, and

thus fails to be properly combinable with, or remedy the deficiency of, the primary references.

The Office Action points to Lambiez et al. "while disclosing doxorubicin-containing liposomes teaches that the inclusion of a negatively charged phospholipid favors the stability of the liposome solution", referring to the Abstract, col. 4, l. 24 et seq., Table II, and the claims. It is accepted that Lambiez et al. teaches the inclusion of a negatively charged phospholipid in liposomes for the encapsulation of doxorubicin. However, the Abstract discloses no liposome-forming materials or ratios, and col. 4, l. 24 et seq. gives only broad guidance, while Example 2 shows 11 formulations of three types, in which the formulation containing PC and PG also contains cholesterol in a ratio PC:PG:cholesterol of 1:1:1. There is no liposomal formulation containing only PC and PG as the lipids. While the Office Action notes, in discussing the previous response, that "the instant claims [i.e. the claims before the present response] do not exclude cholesterol", Applicants note that amended claims 61, 62, 64, 66-73, and 75-81 provide that the lipids consist of EPC and EPG, thereby excluding the presence of cholesterol. Also, Lambiez et al. discloses only the encapsulation of doxorubicin and not the tripeptides of this invention, and only at a lipid:compound ratio of 10:1 (see Examples 2 – 5, at columns 9 and 10). Applicants respectfully submit that while Lambiez et al. does indeed show doxorubicin-containing liposomes, it neither discloses nor suggests the formulation and lipid:compound ratio claimed in claim 61 (and hence the dependent claims and corresponding preparation and use claims) or the encapsulation of small peptides, and thus fails to be properly combinable with, or remedy the deficiency of, the primary references.

Finally, the Office Action points to Uster et al. "while disclosing liposomal formulations for EGF teaches EPC:EPG in equal ratios of 1:1" and that these liposomes enhance the half-life of EGF. It is accepted that Uster et al. teaches the use of liposomes containing 1:1 EPC/EPG, however, only for the encapsulation of epidermal growth factor (EGF) in a gel composition containing either a low-conductivity zwitterionic compound or empty liposomes. EGF is a 53-amino acid polypeptide with 3 disulfide bonds and a molecular weight around 6200. Uster et al. also used their formulation to encapsulate

EGF at a much higher lipid:compound concentration – Table 3 (column18), Liposome I, shows a concentration of EGF of 100 μg/g against EPC and EPG concentrations of 130 mg/g – a lipid:compound ratio of 2600:1, compared to the ratio of 3.5-4.5:0.5-1.5 (2.33:1 – 9:1) claimed in amended claims 61 and 72. Applicants respectfully submit that while Uster et al. does indeed disclose EPC:EPG liposomes having a 1:1 EPC:EPG ratio, it neither discloses nor suggests the lipid:compound ratio currently claimed or the encapsulation of small peptides such as the tripeptides of this invention, so that Uster et al. is not properly combinable with the primary references and if combined does not suggest the formulation of the present claims.

Thus neither of Yau-Young and Lambiez et al. individually, and hence neither in combination, discloses the use of EPC and EPG in a ratio of 0.75-1.25:0.75-1.25 by weight as the sole lipids in the formulation or the encapsulation of small peptides such as the tripeptides of this invention, and therefore they each, individually and collectively, fail to remedy the deficiencies of the primary references. Applicants respectfully submit that, because the primary references "are lacking the teachings of the use of specific liposomes" (Office Action) and because neither Yau-Young nor Lambiez et al. or in combination, fail to disclose or suggest formulations containing EPC and EPG in a ratio of 0.75-1.25:0.75-1.25 as the sole lipids to formulate compounds of formula A or I, or a lipid:compound ratio of 3.5-4.5:0.5-1.5 as shown in amended claims 61 and 72, the claims are patentable over the cited references, which do not disclose or suggest the claimed formulations. Further, the addition of Uster et al. fails to remedy this deficiency because even though Uster et al. discloses 1:1 EPC:EPG liposomes, it does so only in the context of gel formulations of EGF and only at a lipid:compound ratio much higher than that currently claimed.

Applicants respectfully request withdrawal of the rejection as applied to amended claims 61, 62, 64, 66-73, and 75-81.

3. Claims 61-81 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Morgan et al. (*Cancer Chemother. Pharmacol.*, **37**, 363-370, 1996),

further in view of Yau-Young, Lambiez et al., and Uster et al., alone or in combination. The Office Action states that

> "Morgan et al. disclose a method of administration of the claimed compounds to potentiate the effect of chemotherapeutic compounds [locations cited]. What are lacking in Morgan et al are the teachings of the use of liposomes for the delivery of the compounds"

and provides the same discussion with respect to Yau-Young, Lambiez et al., and Uster et al. as provided in the discussion of the rejection over Kauvar et al. and WO 96/40205 in view of these same secondary references.

This rejection as applied to amended claims 61, 62, 64, 66-73, and 75-81 is respectfully traversed.

With regard to the primary reference, it is accepted that Morgan et al. does not anticipate or render unpatentable claims 61, 62, 64, 66-73, and 75-81, the Office Action notes that the reference is lacking "the teachings of the use of liposomes for the delivery of the compounds".

As discussed in the response to the rejection under 35 USC 103(a) over Kauvar et al. or WO 96/40205, further in view of Yau-Young, Lambiez et al., and Uster et al. alone or in combination (paragraph ***2.*** above), neither of Yau-Young and Lambiez et al. individually, and hence neither in combination, discloses the use of EPC and EPG in a ratio of 0.75-1.25:0.75-1.25 by weight as the sole lipids in the formulation or the lipid:compound ratio of 3.5-4.5:0.5-1.5, and therefore they each, individually and collectively, fail to remedy the deficiencies of the primary references; and that Uster et al. also fails to show the lipid:compound ratio and relates to the encapsulation of higher molecular weight polypeptides in gel formulations.

Applicants respectfully request withdrawal of the rejection as applied to amended claims 61, 62, 64, 66-73, and 75-81.

Double patenting rejection

5. Claims 61-81 stand rejected for obviousness-type double patenting over claims 1-38 of Kauvar et al. in view of Yau-Young, Lambiez et al., or Uster et al., alone or in combination. The Office Action states that the

> "the claims in said patent do not recite lipid carrier or specifically negatively charged liposomes as carriers. The patent in the specification however, recites liposomes as carriers."

The Examiner then provides the same discussion with respect to Yau-Young, Lambiez et al., and Uster et al. as provided in the discussion of the rejection of the same claims for obviousness over Kauvar et al. and WO 96/40205 in view of these same secondary references, and concludes that

> "The use of liposomes, negatively charged liposomes for the delivery of the compounds in US 5,955,432 would have been obvious to one of ordinary skill in the art because of the advantages" taught by the secondary references.

This rejection as applied to amended claims 61, 62, 64, 66-73, and 75-81 is respectfully traversed.

Applicants have cancelled claims 63, 65, and 74 and amended claims 61, 62, 64, 66-72, and 79-81. Applicants respectfully submit that claims 61, 62, 64, 66-73, and 75-81 are not double-patented over claims 1-38 of Kauvar et al. in view of Yau-Young, Lambiez et al., or Uster et al., alone or in combination, for the reasons given in paragraph *2.* above responding to a rejection for obviousness of the same claims over the entire disclosure of Kauvar et al. in view of the same combination of secondary references, especially since the claims are silent on liposomal formulations.

Applicants respectfully request withdrawal of the double patenting rejection as applied to amended claims 61, 62, 64, 66-73, and 75-81.

The dependent claims

Since the three rejections made above are on essentially the same basis, i.e. that the primary reference(s) disclose the active ingredients claimed in this application (and Kauvar et al. and WO 96/40205 additionally disclose liposomal formulations), and the

secondary references disclose the claimed liposomal ingredients and ratios, Applicants will discuss the rejections together with respect to the dependent claims.

With respect to claim 64, none of the references disclose or suggest a lipid:compound ratio of 3:1-6:1.

With respect to claims 69-71 and 77-80, none of the references disclose or suggest a formulation with the 1:2:2:7 weight ratio – in fact none of the references disclose or suggest the use of sucrose in the formulation of liposomes.

With respect to claims 71, 76, 78, and 80, none of the references disclose or suggest a lyophilized liposomal formulation.

For these additional reasons, dependent claims 64, 69-71, and 77-80 (and claim 81 to the extent it is dependent on these claims) are believed patentable.

Conclusion

Entry of the amendment, examination, and allowance of claims 61, 62, 64, 66-73, and 75-81 are respectfully requested.

If the Examiner believes that a conversation with the undersigned agent would aid in advancing the prosecution of this case, the Examiner is requested to call the undersigned at (650) 843-5245.

Dated: March 22, 2005

Respectfully submitted,

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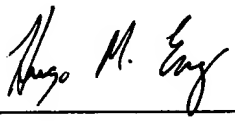
By: 

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